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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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HUYNH, PHUONG N	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/980,516	BERGERON ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-10,12-20 and 24-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *9* is/are allowed.

6)☒ Claim(s) *4-8,10,12-20 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 4-10, 12-20, and 24-27 are pending.

2. In view of the amendment filed 6/6/07, the following rejections remain.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 4-8, 12-16, 19-20 and 24-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,773,027 (of record, issued June 30, 1998; PTO 892) in view of Catin et al (of record, J Virology 71(3): 1922-1930, March 1997; PTO 892).

The '027 patent teaches various formulations for treatment of viral disease such as HIV which comprise an antibody coupled to various liposomes such as liposome that comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10:1 and 1:1, wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length (palimitoyl is 16 carbons while stearoyl is 18 carbons in length) (See claim 1 of '027 patent, col. 3, lines 58-62, in particular). The '027 patent further teaches liposome comprising a polyethyleneglycol derivative of diacylphosphatidylethanolamine (see claim 2 of '027 patent, in particular). The reference formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine and wherein the

polyethyleneglycol has a molecular weight between about 500 and 5000 Daltons (See claim 11 of '027 patent, in particular). The '027 patent also teaches a formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine (DPPC) and diacylphosphatidylglycerol (DSPG) in a molar ratio of 10:3 (See col. 3, lines 46-47, in particular). The '027 patent teaches another formulation wherein the liposome (lipid component) comprises a mixture of diacylphosphatidylcholine (DPC): diacylphosphatidylglycerol (DPG): diacylphosphatidylethanol-amine-polyethyleneglycol (DPE-PEG) in a molar ratio of 10:3:1.45 (See col. 5, lines 48, col. 9, Table 3, line 39, in particular). The reference molar ratio of 10: 3:1.45 is within the claim range of 10:3:0.1-3. The reference formulation further encapsulated a drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for treating viral infection (See claims 7, 9-10 of '027 patent, in particular). The '027 patent further teaches that the reference liposome formulation can be modified by coupling of antibody molecules to enhance the targeting of the liposome to the specific cells (See col. 4, lines 11-13, in particular) that are HIV reservoirs as well as marked improvement of the pharmacokinetics of drugs (See abstract, in particular). The advantages of targeted delivery of anti-viral agents encapsulated in liposome are that it could increase efficacy by reducing toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improving drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as reducing the frequency of administration of anti-HIV agents and therefore improving the quality of life of patients with AIDS and other viral diseases as taught by the '027 patent (See col. 2, lines 25-31, col. 9, lines 7-12, in particular). The drug-liposome formation also increases the drug uptake by macrophages such as RAW 264.7 (see col. 7, lines 4-8, in particular).

The claimed invention differs from the teachings of the reference only in that the formulation which comprises an anti-HLA-DR antibody instead of any antibody coupled to the liposome wherein the formulation capable of binding to an HLA-DR protein present at both the surface of an infectious agent and at the membrane surface of a cell.

Catin et al teach antibody such as anti-HLA-DR 2.06 (class II MHC) that binds to HLA protein present at the surface of an infectious agent such as HIV-1 virions and at the surface of a host cell membrane such as CD4+ T cells and macrophage (see entire document, page 1923, col. 2, Antibodies, page 1925, col. 1, page, in particular). Catin et al teach infectious agent such as HIV acquired host protein such as HLA-DR, ICAM-1 (CD54), CD55 (DAF), CD59, CD63 and CD71 (see page 1922, col. 1, in particular). Catin et al teach antibody to HLA-DR or anti-LFA-1

(CD11a) inhibits HIV infection since HIV virus acquired host cellular protein on the surface of the progeny virus (see page 1922, col. 1, in particular). Catin et al further teach CD4 molecule is the primary cell surface receptor for HIV-1 (page 1922, col. 2, in particular). Catin et al teach HLA-DR protein is one of the most abundant host derived protein acquired by virus such as HIV-1 and HIV-2 (see page 1922, col. 2, in particular). The reference HLA-DR protein is expressed in lymphoid cells such as CD4+ T lymphocytes, and monocyte derived macrophages or antigen presenting cells within the reticuloendothelial system (lymph node) (see page 1922, col. 2, in particular). Catin et al teach HIV-1 infectivity is enhanced by the presence of virally incorporated host cell membrane (see page 1925, col. 2, last paragraph, page 1927, col. 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody coupled to a liposome that comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in the formulation as taught by the '027 patent for the specific anti-HLA-DR antibody that binds to HLA-DR on the surface of infectious agent and host cells as taught by the Catin et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '027 patent teaches coupling of antibody molecule to a liposome enhances the targeting of the drug encapsulated in the liposome to the specific cells that are HIV reservoirs as well improving the pharmacokinetics of drugs (See col. 4, lines 11-13, abstract, in particular). Catin et al teach HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 and HLA-DR protein is expressed on the surface of host lymphoid cells such as CD4+ T lymphocytes, and monocyte derived macrophages which are an obvious target for such strategy (see page 1922, col. 2, in particular).

Applicants' arguments filed 6/6/07 have been fully considered but are not found persuasive.

Applicants' position is that the cited references fail to teach or suggest Applicant's formulation that comprises an anti-HLA-DR antibody coupled to a liposome, which is capable of binding to an HLA-DR protein present on both the surface of an infectious agent *and* at the membrane surface of a cell. The Examiner cites to Bergeron for teaching a formulation for treating a viral disease such as HIV that comprises a liposome composed of a mixture of

diacylphosphatidylcholine and diacylphosphatidylglycerol, including coupling of antibody molecules to the liposome to enhance targeting of the liposome to specific cells, citing to col. 4, lines 11-13. The Examine maintains that it would be obvious to substitute an anti-HLA-DR antibody as disclosed by Cantin in the formulation taught by Bergeron. The Examiner further asserts that one skilled in the art would have a reasonable expectation of success in producing the claimed invention based on the combined teachings of the references - Bergeron and Cantin.

Bergeron describes antiviral agents encapsulated in liposome. The only reference to the use of antibodies is a *general statement* at col. 4, lines 9-14, that liposome-encapsulated drugs include imrnunoliposomes that are "modified by the coupling of antibody molecules which enhance the targeting of specific *cells."* Bergeron provides no examples of any antibodies and no teaching of how such coupling is achieved. Other than a general statement, Bergeron provides no guidance or other information that would lead to Applicant's invention.

Furthermore, the statement in Bergeron relates only to antibody molecules that enhance *targeting of specific cells.* Bergeron says nothing about antibodies to target an infectious agent. The Examiner cites Cantin for teaching an anti-HLA-DR antibody 2.06 that binds to the surface of HIV-1 virions *and* a host cell membrane (see Office Action at page 5, emphasis added): Catin et al teach antibody such as anti-HLA-DR 2.06 (class II MHC) that binds to HLA protein present at the surface of an infectious agent such as HIV-1 virions *and at the surface Of a host cell membrane* such as CD4+ T cells and macrophage (see entire document, page 1923, col. 2, Antibodies, page 1925, col. 1... in particular). The Examiner's interpretation of Cantin is incorrect.

First of all, Cantin describes reacting 2.06 only with HIV-1 particles. Cantin does *not* disclose reacting *2.06* with *cells - or* reacting *a liposome-bound 2.06* with *viral particles and much less cells.* Rather, Cantin discloses reacting antibody L243~ with cells - transfected 293 T cells (single MHC-II isotype, HLA-DR1). See page 1923, col. 2 (Flow cytometric analysis of cell surface and internal antigens).

Secondly, Cantin describes reacting 2.06 with specially produced virus stock2 expressing a MHC-II isotype - namely the HLA-DR1 allele (see pp. 1928-1929, bridging sentence). Cantin does not disclose reacting antibody with HIV-1 virions from primary isolates, macrophages, or blood plasma, for example, which would include the highly polymorphic HLA-DR locus, nor cells that express all MHC-II isotypes (DR, DP, DQ) on their surfaces. Cantin particularly states that the described work does not relate to infectivities of virions on primary

monocyte-derived macrophages (page 1928, 2"d col.): In this work, we have not tried to compare the infectivities of virions bearing or not bearing HLA-DR1 on primary monocyte-derived macrophages...These studies are needed, since monocytes/macrophayes are also infected in vivo with HIV and are thought to play a key role in the pathogenesis of the disease... Moreover, virally infected monocytes/macrophages are potent producers of HLA-DR bearing virions because they are known to express on their surfaces all MHC-II isotypes (DR, DP, and DQ)...

As acknowledged by Cantin, the HLA-DR locus is highly polymorphic, and the affinity between HLA-DR and CD4 on a cell surface may vary according to the HLA-DR allele (p. 1929, col. 1). See also, Cantin at pp. 1928-1929, bridging sentence ("...this work focused on a single HLA-DR allele, namely HLA-DRI ..."). At page 7, paragraph, the Examiner stated (emphasis added): In fact, the same monoclonal antibody anti-HLA-DR (clone 2.06, IgG1) as taught by Cantin et al was used by applicants, see instant specification at pages 12, lines 7-8. One skilled in the art reading the specification would expect a monoclonal anti-HLA-DR 2.06 antibody from the same clone would necessarily and inevitably bind to the same HLA-DR protein on both host cell expressing HLA-DR and on HIV virions that have incorporated the host HLA-DR protein.

It is clear from the foregoing statement that the Examiner is impermissibly utilizing Applicant's disclosure as a guide for combining the references. It is also clear that it is only through hindsight reconstruction utilizing Applicant's disclosure, that the Examiner can say that the cited references teach a formulation of liposomes coupled to an antibody to target *both* ceils and virus. The Examiner has given no good basis why a skilled artisan with no knowledge of the invention, would select the elements from the cited references for combination in the manner claimed.

One skilled in the art reading Bergeron would not be motivated to utilize antibody 2.06 of Cantin for coupling to the described liposome-enclosed drugs. Bergeron generally teaches coupling an antibody to liposomes to enhance targeting of specific *cells*. By comparison, Cantin discloses use of antibody 2.06 to target special *HIV-1 particles --not cells.*

Furthermore, based on Cantin's disclosure, one skilled in the art would not expect monoclonal anti-HLA-DR1 2.06 antibody would necessarily and inevitably bind to HLA-DR *protein* on *both host cells* expressing *HLA-DR protein and* on *HIV virions* that have incorporated the host HLA-DR *protein* - much less an anti-HLA-DR antibody coupled to a liposome.

This is further supported by Saarloos -*as acknowledged by the Examiner* (Office Action at page 6, emphasis added): ... Saarloos et al. discloses that HLA-DR (Class II MHC) was

associated with *in vivo* sources of HIV-I virions from primary isolates, macrophages and blood plasma using an immunocapture method with an anti-HLA-DR antibody, the results showed that the anti-HLA-DR antibody captured about 50% of HIV Ada-M and HIVBa-L monocytotropic virus, and four of eight samples of plasma virus did not detectably bind to the anti-HLA-DR antibody (See Saarloos at page 1641, 2"d col., 2, 2"d ¶). At most, Saarloos' disclosure presents an "obvious-to-try" situation. *Given the unpredictability of the binding of an anti-HLA-DR antibody with HIV-1 virion~ and the level of HLA-DR expression of monocytes according to Saarloos, one skilled in the art reading Saavloos' disclosure would not expect an anti-HLA-DR antibody would necessarily and inevitably bind to HLA-DR protein on both a cell and on HIV virus ~ much less an antibody coupled to a liposome.*

Saarloos discloses that HLA-DR (Class II MHC) was associated with *in vivo* sources of HIV-1 virions from primary isolates, macrophages and blood plasma using an immunocapture method with an anti-HLA-DR antibody. However, the results showed that the anti-HLA-DR antibody captured only abut 50% of HIVMa-M and HIVBa-L monocytotropic virus, and four of eight samples *of plasma virus did not detectably bind* to the anti-HLA-DR antibody (Saarloos at page 1641, 2"d col., 2nd).

In response, the claims encompass a formulation comprising anti-HLA-DR immunoliposome wherein the anti-HLA-DR antibody or binding fragment thereof is coupled to a liposome which comprises a mixture of diacylphophosphatidylcholine and diacylphosphatidylglycerol in a molar ratio of between 10: 1 to 1:1 and the acyl chains are either saturated or unsaturated and 14-18 carbon atoms in length.

The '027 patent (Bergeron et al) teaches immunoliposome comprising antibody coupled to liposome which comprises a mixture of diacylphophosphatidylcholine and diacylphosphatidylglycerol in a molar ratio of between 10: 1 to 1:1 and the acyl chains are either saturated or unsaturated and 14-18 carbon atoms in length.

The claimed invention differs from the teachings of the reference only in that the antibody is an anti-HLA-DR antibody or binding fragment thereof coupled to the liposome.

However, Catin et al teach antibody such as anti-HLA-DR 2.06 (class II MHC) that binds to HLA-DR (see entire document, page 1923, col. 2, Antibodies, page 1925, col. 1... in particular).

In response to applicant's argument that the '027 patent provides no examples of any antibodies and no teachings of how such coupling is achieved, it was well known in the art at the

time the invention was made to coupled antibody to liposome as evidenced by the teachings of Desormeaux et al (of record, J Drug Targeting 6(1): 1-15, 1998; PTO 1449). The specification/patent need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

In response to applicant's argument that Cantin does not describe reacting the anti-HLA DR antibody to 2.06 with HIV-1 virions from primary isolates, macrophages, or blood plasma, none of the claims recite "reacting the anti-HLA DR antibody to 2.06 with HIV-1 virions from primary isolates, macrophages, or blood plasma" as argued. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e.,) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Further, a product is a product, irrespective of its intended use. The reference antibody anti-HLA-DR antibody 2.06 binds to HLA-DR protein, regardless whether HLA-DR is isolated from a cell or expressed by an infectious agent or expressed on the membrane of the a cell. The binding specificity of the reference antibody is an inherent property of the antibody. It is irrelevant to the claimed invention whether HLA-DR1 locus is highly polymorphic and the affinity between HLA-DR and CD4 on cell surface vary.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971).

With respect to the argument that formulation of liposome coupled to an antibody to target both cells and virus, and the Examiner has given no good basis why a skilled artisan with no knowledge of the invention would select the elements from the cited references for the

combination in the manner as claimed, it is within the purview of one ordinary skill in the art at the time the invention was made that HIV virus acquired host protein such as HLA-DR as taught by Cantin et al and antibody that binds to host protein such as HLA-DR coupled to liposome would be expected to bind to both the virus that acquired the host protein and the host cell that expressed the HLA-DR protein.

In contrast to applicant's assertions of the rejection is based upon an "obvious-to-try" standard, it is by now well understood that the ultimate conclusion of law that claimed subject matter as a whole would have been obvious under 35 USC 103 may at times properly be drawn from an inference of fact arising from prior art teachings which could be considered an inference that it would be "obvious to try" that which is claimed. In re O'Farrell, 853 F.2d 894, 7 USPQ 2d 1973 (Fed. Cir. 1988); Contour Saws Inc. v. Starrett Co., 444 F. 2d 433, 170 USPQ 433 (Ct.App. 1977); In re Marzocchi, 439 F. 2d 220, 169 USPQ 367 (CCPA 1977); In re Lindell, 385 F. 2d 435, 155 USPQ 521 (CCPA 1967). The evidence of purported unobvious results of record in this application is insufficient to overcome the inference of fact in this case. Therefore the above claims remain rejected under 35 USC 103 for the reasons above and also those set forth in the previous Office action.

6. Claims 10 and 17-18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,773,027 (of record, issued June 30, 1998; PTO 892) in view of Catin et al (of record, J Virology 71(3): 1922-1930, March 1997; PTO 892) as applied to claims 4-8, 12-16, 19-20 and 24-27 mentioned above and further in view of Desormeaux et al (of record, J Drug Targeting 6(1): 1-15, 1998; PTO 1449).

The combined teachings of the '027 patent and Catin et al have been discussed supra. Catin et al further teach CD4 molecule is the major cellular receptor for HIV-1 for viral entry into host cell during the infection process and the CD4 is also a natural ligand of HLA-DR (see page 1927, col. 1, Discussion, in particular).

The invention in claim 10 differs from the combined teachings of the references only in that the formulation further comprising additional antibody that binds to CD4.

The invention in claim 17 differs from the combined teachings of the references only in that the formulation further comprising an additional antibody molecule that binds to one or more CD4 proteins.

The invention in claim 18 differs from the combined teachings of the references only in that the formulation further comprising an additional antibody molecule that binds to one or more CD4 proteins.

Desormeaux et al teach a formulation which comprises antibody and binding fragment thereof such as $F(ab)_2$ that bind specifically to CD4 molecules expressed on infectious agent such as HIV virus and CD4+ T cells and wherein the reference antibody or $F(ab)_2$ is coupled to a liposome for targeting liposome containing drug to CD4+ T cells, macrophages and viral particles (See entire document, abstract, page 3, col. 1, page 7, col. 1, last paragraph, in particular). The reference formulation further comprises an anti-viral drug such as AZT, ddC, foscanet, ddITP, (see page 3, col. 1, Drug containing liposome against HIV infection, in particular). Desormeaux et al further teach the advantage of using antibody binding fragment by removing the Fc fragment of an antibody instead of a whole antibody is that it reduces the immunogenicity of the antibody in immunoliposomes upon repeated administration (see page 6, col. 2, in particular). Desormeaux et al teach it is now well-established that CD4+ T cells and macrophages are the main reservoirs for HIV in infected individual and the advantage of using antibody directed liposome as a sustained drug carriers is that it target specific delivery of drugs encapsulated liposome to viral particles, macrophages and/or T cells in the lymphoid tissues (see page 11, col. 1, paragraph bridging pages 7 and 8, in particular). Desormeaux et al teach that site-specific drug targeting may allow less frequent administrations of anti-viral agents and at lower doses (therefore reduced toxicity) than convention therapy, and thereby improving efficacy, and quality of life for patients (see page 11, Advantages and Limitations, Table 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include additional antibody such as anti-CD4 or binding fragment thereof that binds to one or more CD4 proteins acquired by the infectious HIV and CD4 expressed on the surface of host cells as taught by Desormeaux et al in the formulation comprising an anti-HLA-DR antibody molecule coupled to a liposome as taught by the '027 patent and Catin et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Catin et al teach CD4 molecule is the major cellular receptor for HIV-1 for viral entry into host cell during the infection process and the CD4 is also a natural ligand of HLA-DR (see page 1927, col. 1, Discussion, in particular). Desormeaux et al teach it is now well-established that CD4+ T

cells and macrophages are the main reservoirs for HIV in infected individual and formulation which comprises anti-CD4+ antibody or antibody binding fragment such as $F(ab)_2$ capable of targeting liposome encapsulated anti-viral drug to those viral reservoirs should lead to a reduction in the dissemination of HIV from the lymphoid tissue and to a preservation of the follicular dendritic cells microenvironment that would likely protect the infected host from developing the characteristic immunodeficient state (see paragraph bridging pages 7 and 8, in particular). Desormeaux et al teach that site-specific drug targeting may allow less frequent administrations of anti-viral agents and at lower doses (therefore reduced toxicity) than convention therapy, and thereby improving efficacy, and quality of life for patients (see page 11, Advantages and Limitations, Table 1, in particular). The '027 patent teaches coupling of antibody molecule to the liposome enhances the targeting of the drug encapsulated liposome to the specific cells that are HIV reservoirs as well as marked improvement of the pharmacokinetics of drugs (See col. 4, lines 11-13, abstract, in particular). Catin et al teach HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2; HLA-DR protein is expressed on the surface of host lymphoid cells such as CD4+ T lymphocytes, and monocyte derived macrophages which are an obvious target for such strategy (see page 1922, col. 2, in particular).

Applicants' arguments filed 6/6/07 have been fully considered but are not found persuasive.

Applicants' position is that the added disclosures of Desormeaux and/or Harlow do not make up the deficiency of Bergeron with Catin.

In response, the arguments with respect to the deficiency of Bergeron with Catin have been discussed supra and are incorporated here by reference.

7. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,773,027 (of record, issued June 30, 1998; PTO 892) in view of Catin et al (of record, J Virology 71(3): 1922-1930, March 1997; PTO 892) as applied to claims 4-8, 12-16, 19-20 and 24-27 mentioned above and further in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629) and Desormeaux et al (of record, J Drug Targeting 6(1): 1-15, 1998; PTO 1449).

The combined teachings of the '027 patent and Catin et al have been discussed supra.

The invention in claim 20 differs from the teachings of the references only in that the formulation which comprises an anti-Fab' antibody fragment against a HLA-DR instead of a whole antibody against HLA-DR.

Harlow *et al* teach a method of producing antibody fragment such as Fab fragment (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Desormeaux et al teach the advantage of using antibody binding fragment by removing the Fc fragment of an antibody instead of the whole antibody when coupled to liposome is that it reduces the immunogenicity of the immunoliposome (antibody coupled immunoliposome) upon repeated administration (see page 6, col. 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as Fab' as taught by Harlow et al using the whole anti-HLA-DR antibody as taught by Catin et al and then coupling the antibody fragment to the liposome which comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10:1 and 1:1, wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length as taught by the '027 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to use antibody fragment instead of a whole antibody when coupled to liposome is that it reduces the immunogenicity of the immunoliposome (antibody coupled immunoliposome) upon repeated administration as taught by Desormeaux et al (see page 6, col. 2, in particular). Harlow *et al* teach that fragments of antibodies can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular). The '027 patent teaches coupling of antibody molecule to the liposome enhances the targeting of the drug encapsulated liposome to the specific cells that are HIV reservoirs as well as marked improvement of the pharmacokinetics of drugs (See col. 4, lines 11-13, abstract, in particular). Catin et al teach HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 and HLA-DR protein is expressed on the surface of lymphoid cells such as

CD4+ T lymphocytes, and monocyte derived macrophages which is an obvious target for such strategy (see page 1922, col. 2, in particular).

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Applicants' arguments filed 6/6/07 have been fully considered but are not found persuasive.

Applicants' position is that the added disclosures of Desormeaux and/or Harlow do not make up the deficiency of Bergeron with Catin.

In response, the arguments with respect to the deficiency of Bergeron with Catin have been discussed supra and are incorporated here by reference.

8. The following new ground of objection and rejection are necessitated by the amendment filed 6/6/07.

9. Applicant is advised that should claims 24 and 25 be found allowable, claims 26 and 27 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The recitation of "***about*** 10:3" in amended claim 6 represents a departure from the specification and the claims as originally filed. This is because the specification discloses the formulation wherein the liposome comprises diacylphosohatidylcholine and

diacylphosphatidylglycerol wherein the molar ratio is **10:3**. The specification at page 7, lines 6-7 discloses the formulation wherein the liposome comprises dipalmitoylphosphatidylcholine (DPPC):dipalmitoylphosphatidylglycerol (DPPG) in a molar ratio of 10:3. The term "**about**" broadening out said ratio and has no support in the specification and claims as originally filed.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the limitation "molar ratio is 10:**3**". There is insufficient antecedent basis for this limitation in the claim. This is because base claim 24 recites "molar ratio of 10:**1** to 1:**1**".

14. Claim 9 is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone

are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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